REMARKS

Claims 1-18 are pending in the subject application. By this Amendment, applicants have cancelled claims 1-5, 8 and 10-15 without disclaimer or prejudice, and added new claims 175-184.

Applicants have amended claims 6 and 16 to more specifically characterize the polypeptide domains to which antibodies bind. The amendments to claims 6 and 16 are supported in the specification at, *inter alia*, page 173, lines 20-27 and page 175, line 34 to page 176, line 5. Applicants have also rewritten claims 9 and 18 in independent form to make them allowable as indicated they would be by the Examiner.

Support for new claims 175-184 may be found, *inter alia*, in the subject specification as follows: Claim 175, page 21, lines 17-25; page 82, lines 19-27; Claim 176, page 21, lines 17-25; page 56, lines 13-17 and 21-25; page 57, lines 27-31 and line 35 to page 58, line 2; page 82, lines 19-27 and line 35 to page 83, line 8; Claim 177, page 21, lines 17-25; page 56, lines 17-19; page 57, lines 31-33; page 68, lines 14-15; page 69, lines 27-28; page 82, lines 19-27; Claim 178, page 21, lines 17-25; page 56, lines 17-20; page 57, lines 31-34; page 82, lines 19-27; Claim 179, page 21, lines 17-25; page 56, lines 17-20; page 57, lines 31-34; page 82, lines 19-27; Claim 180, page 21, lines 17-25; page 56, lines 17-21; page 57, lines 31-35; page 68, lines 14-15; page 69, lines 27-28; page 82, lines 19-27; Claim 181, page 21, lines 17-25; page 56, lines 27-29; page 58, lines 4-6; page 82, lines 19-27; Claim 182, page 21, lines 17-25; page 57, lines 6-7; page 58, lines 21-22; page 59, lines 9-26; page 62, line 23 to page 63, line 2; page 65, line 25 to page 66, line 4; page 82, lines 19-27; Claim 183, page 21, lines 17-25; page 61, lines 1-

25; page 64, lines 1-22; page 67, lines 4-30; page 82, lines 19-34; and Claim 184, page 21, lines 17-25; page 57, lines 7-10; page 58, lines 23-25; page61, lines 27-29; page 63, lines 4-7; page 64, lines 29-31; page 66, lines 6-9; page 67, lines 32-34; page 82, lines 19-27.

Applicants maintain that neither the amended claims nor the new claims raise any issue of new matter since they are fully supported by the specification as filed. Accordingly, upon entry of this Amendment, claims 6, 7, 9, 16-18 and 175-184 will be pending.

Objections to the Specification

On page 2 of the April 30, 2003 Final Office Action, the Examiner stated that the disclosure is objected to because of the following informalities which required appropriate correction: corresponding SEQ ID Nos. are missing from the sequences in the specification; on page 95, lines 22-23, the specification refers to the TIP-2 "amino acid sequence shown in Figure 23" but Figure 23 does not show any amino acid sequence; and the abstract of the disclosure exceeds 150 words.

In response, applicants have hereinabove amended the specification to address the Examiner's remarks as follows: SEQ ID Nos. have been added to sequences in the specification and the abstract has been shortened to less than 150 words. Also, the reference to Figure 23 on page 95 of the subject application has been changed to Figure 29. No new matter has been added by this amendment which is supported by Figure 29 as filed.

Allowed Claims

Applicants acknowledge with appreciation the Examiner's statement on page 8, paragraph 13 of the Final Office Action that claims 7 and 17 are in condition for allowance.

Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 6, 8 and 10-16

The Examiner rejected claims 1, 2, 8 and 10-15 under 35 U.S.C. §103(a) as allegedly unpatentable over De Vries et al. (PNAS 95: 12340-12345, 1998) and Rousset et al. (Oncogene 16: 643-654, 1998) and as evidenced by the specification, and further in view of Campbell (Monoclonal Antibody Technology, Elsevier Science Publishers, pages 1-32, 1986) and Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, page 322, 1988).

In response to the rejection of claims 1, 2, 8 and 10-15, applicants maintain that the Examiner has failed to establish a *prima facie* case of obviousness of these claims. In response to the rejection of claims 6 and 16, applicants respectfully traverse. Claims 6 and 16, as amended, provide monoclonal antibodies. The antibody of claim 6 specifically binds and forms a complex with TIP-2 antigen located on the surface of human cancer cells, wherein the monoclonal antibody binds to the same extracellular domain of TIP-2 as does monoclonal antibody 27.B1 produced by hybridoma 27.B1 (ATCC Designation No. PTA-1599). The antibody of claim 16 specifically binds and forms a complex with TIP-2 antigen located on the surface of human cancer cells, wherein the monoclonal antibody binds to the same extracellular

domain of TIP-2 as does monoclonal antibody 27.F7 produced by hybridoma 27.F7 (ATCC Designation No. PTA-1598).

Applicants note that the Examiner's analysis relies heavily on a generic statement in Campbell, page 29, that "[i]t is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)." By the Examiner's logic regarding this statement in Campbell, the prior identification of a protein *per se* would necessarily preclude the possibility of obtaining a patent on either a cloned gene encoding, or an antibody directed to, that protein. However, applicants respectfully point out to the Examiner that that view has been firmly repudiated by the Federal Circuit:

> Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or make it obvious to prepare a cDNA, that does not make obvious a particular claimed cDNA. "Obvious to try" has long been held not to constitute obviousness. (*In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210)

Consistent with *Deuel*, applicants maintain that a teaching of a protein and a general experimental approach to making antibodies cannot reasonably be construed as making obvious a monoclonal antibody that binds to distinct domains of the protein, absent a specific motive.

Applicants note further that TIP-2 protein was identified and characterized independently by De Vries et al. and Rousset et al. in 1998. The fact that, five years later, the Examiner has not identified a teaching of TIP-2 antibodies produced by either De Vries et al. or Rousset et al. or by anyone one else, other than by applicants in this invention, is at odds with the cited

statement in Campbell and with the Examiner's position.

The Examiner also maintains that the term "domain" in claims 6 and 16 is allegedly indefinite. The Examiner interpreted the term as meaning any part of the protein to which the antibodies 27.B1 and 27.F7 bind, which includes cross reactivity. Accordingly, he stated that it would have been obvious that in making the monoclonal antibodies against the entire TIP-2 protein this would result in antibodies binding to all regions of the protein and as such to all the "domain[s]" of TIP-2.

In response, applicants respectfully maintain that "domain" is a term of art that is understood to mean a distinct structural or functional portion of a protein. Thus, by definition, a polypeptide domain comprises less than the entire polypeptide, and it is therefore improper to refer, as the Examiner has done, to an antibody binding to "all the domain[s]" of TIP-2. Applicants note further that the specification clearly indicates that the 27.B1 and 27.F7 antibodies bind to extracellular and cytoplasmic domains, respectfully, of cell surface-associated TIP-2 antigen.

Applicants respectfully submit that in view of the above remarks, the cited art fails to teach all elements of the invention and to create a motive to combine. Accordingly, applicants maintain that claims 6 and 16 satisfy the requirements of 35 U.S.C. §103(a), and request that the Examiner withdraw this rejection.

Claims 1-6, 8 and 10-16

The Examiner rejected claims 1-6, 8 and 10-16 under 35 U.S.C. §103(a) as allegedly unpatentable over De Vries et al. (PNAS 95:

12340-12345, 1998) and Rousset et al. (Oncogene 16: 643-654, 1998) and as evidenced by the specification, and further in view of Campbell (Monoclonal Antibody Technology, Elsevier Science Publishers, pages 1-32, 1986) and Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, page 322, 1988) as applied to claims 1, 2, 8 and 10-15, and further in view of Adair et al. (WO 91/09967, published 7/11/91) and Green et al. (Nature Genetics 7: 13-21, 1994) of record.

The Examiner also rejected claims 6 and 16 because of the previous amendment to these claims reciting "domain" and the allegedly indefinite nature of this term. The Examiner interpreted the term as meaning any part of the protein to which the antibodies 27.B1 and 27.F7 bind, which includes cross reactivity. The Examiner reiterated his arguments made in relation to the above-described rejection of claims 1-6, 8 and 10-16 under 35 U.S.C. §103(a), and stated that since TIP-2 is associated with an oncoprotein, it would be obvious to produce a human, humanized, or chimeric antibody to the protein.

In response to the rejection of claims 1-5, 8 and 10-15, and without conceding the correctness of the Examiner's position, applicants again note that claims 1-5, 8 and 10-15 have been cancelled.

With regard to claims 6 and 16, applicants respectfully traverse for the reasons set forth above. Applicants also maintain that the term "domain" is not indefinite and does not refer to "any part" of the protein to which the antibodies 27.B1 and 27.F7 bind. Rather, the ordinary meaning of "domain," consistent with the use of the term in the instant specification, refers to a distinct structural or functional portion of a protein which

comprises less than the entire protein. The specification indicates that the 27.B1 and 27.F7 antibodies bind to extracellular and cytoplasmic domains respectfully, of cell surface-associated TIP-2 antigen. Applicants note that amended claims 6 and 16 provide antibodies wherein these binding features are inherent.

In view of the above remarks, applicants maintain that claims 6 and 16 satisfy the requirements of 35 U.S.C. §103(a).

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 6 and 16 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to distinctly point out and distinctly claim the subject matter which applicants regard as the invention. According to the Examiner, claims 6 and 16 are indefinite for reciting "binds to the same domain of TIP-2" because the phrase allegedly is not clear. The Examiner stated that it is not clear to what the term "domain" is referring since the specification does not clearly define the term. The Examiner posed the question whether the "domain" is the entire protein [TIP-2] or some specific region of the protein.

In response, applicants respectfully traverse the Examiner's rejection. Applicants maintain that the term "domain" is a term of art that is understood by one skilled in the art to refer to a distinct structural or functional portion of a protein that comprises less than the entire polypeptide. In support of this assertion, applicants note the following definition of "domain."

"A discrete portion of a protein with its own function. The

> combination of domains in a single protein determines its overall function." (BioTech Life Science Dictionary, available at http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=domain).

A copy of this definition is attached hereto as **Exhibit B**.

Applicants contend that it was not necessary to specifically define this term of art in the subject specification since its usage in the specification is consistent with its ordinary meaning that is well-known to one skilled in the biological arts. In light of this well-known meaning of "domain," applicants submit that the answer to the Examiner's query as to whether the term refers to the entire protein or to some specific region of the protein is clearly that it refers to a structural or functional portion of the overall polypeptide.

With reference to the different domains bound by the 27.F7 and 27.B1 antibodies, applicants note that, as described in the specification, antibody 27.B1 binds to a region of TIP-2 on the surface of breast cancer cells whereas antibody 27.F7 binds to a different region of TIP-2 that is intracellularly located (see specification, page 170, lines 33-37; page 173, lines 20-27; page 175, line 34 to page 176, line 5). Given this information, one skilled in the art would immediately understand that TIP-2 protein contains at least an extracellular domain to which 27.B1 binds and an intracellular or cytoplasmic domain to which 27.F7 binds. These features are inherent in the antibodies of amended claims 6 and 16.

In view of the above remarks, applicants maintain that claims 6 and 16, as amended, satisfy the requirements of 35 U.S.C. §112,

second paragraph.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 6 and 16 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner stated claims 6 and 16 had been amended to recite "domain" but he could find no apparent support for the term in the specification. The Examiner required applicants to provide specific support for the limitation or remove it from the claims.

In response, applicants respectfully traverse the Examiner's rejection of claims 6 and 16 under 35 U.S.C. §112, first paragraph. As discussed above, applicants contend that the term "domain" is a term of art that is understood by one skilled in the art to refer to a distinct structural or functional portion of a protein. The term "domain" is used repeatedly in the instant specification (see pages 169-170 and 173-175) in a manner entirely consistent with this ordinary meaning of the term. Applicants note that nothing in the specification suggests that the term is used in any context other than its ordinary meaning.

Moreover, the specification also states that the 27.B1 antibody binds to an epitope of TIP-2 on the surface of breast cancer cells whereas the 27.F7 antibody binds to a different epitope of TIP-2 that is intracellularly located (see specification, page 170, lines 33-37; page 173, lines 20-27; page 175, line 34 to page 176, line 5). Though the specification does not explicitly

state that the two antibodies bind to different "domains," it would be clear to one skilled in the art that cell surface-associated TIP-2 protein contains at least an extracellular domain to which 27.B1 binds and an intracellular or cytoplasmic domain to which 27.F7 binds. Thus, applicants maintain that the recitation of "domain" in claims 6 and 16 is supported by the specification.

Applicants respectfully submit that claims 6 and 16, as amended, satisfy the requirements of 35 U.S.C. §112, first paragraph.

New Claims:

Applicants respectfully submit that new claims 175-184 would not create an undue burden on the Examiner to search, in view of the search already performed on the presently claimed antibodies, since the diagnostic kits incorporate the same type of antibodies.

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit C**), and attached hereto as **Exhibits 1-34**, respectively:

1. U.S. Patent No. 6,197,582, issued to Ilya Trakht on March 6, 2001 (**Exhibit 1**);

2. PCT International Application No. PCT/US99/05828, filed March 18, 1999, International publication No. WO 99/47929,

published September 23, 1999, on behalf of the Trustees of Columbia University in the City of New York (**Exhibit 2**);

3. Antonov AS, Nikolaeva MA, Klueva TS, Romanov YuA, Babaev VR, Bystrevskaya VB, Perov NA, Repin VS, Smirnov VN (1986) Primary culture of endothelial cells from atherosclerotic human aorta. Part 1. Identification, morphological and ultrastructural characteristics of two endothelial cell subpopulations. Atherosclerosis 59: 1-19 (**Exhibit 3**);

4. Berman DM, Gilman AG (1998) Mammalian RGS proteins: barbarians at the gate. J Biol Chem 273: 1269-1272 (**Exhibit 4**);

5. Borrebaeck CA, Danielsson L, Moller SA (1987) Human monoclonal antibodies produced from L-leucine methyl ester-treated and in vitro immunized peripheral blood lymphocytes. Biochem Biophys Res Commun 148: 941-946 (**Exhibit 5**);

6. Brodin T, Olsson L, Sjogren HO (1983) Cloning of human hybridoma, myeloma and lymphoma cell lines using enriched human monocytes as feeder layer. J Immunol Methods 60: 1-7 (**Exhibit 6**);

7. Casali P et al. (1986) Science 234: 476-479 (**Exhibit 7**);

8. Galanos G et al. (1969) Eur J Biochem 9: 245-249 (**Exhibit 8**);

9. Glassy MC, Handley HH, Hagiwara H, Royston I (1983) UC 729-6, a human lymphoblastoid B-cell line useful for generating antibody-secreting human-human hybridomas. Proc Natl Acad Sci (USA) 80: 6327-6331 (**Exhibit 9**);

10. Goldman-Leikin RE, Salwen HR, Herst CV, Variakojis D, Bian ML et al. (1989) Characterization of a novel myeloma cell line, MM.1. J Lab Clin Med 113: 335-345 (**Exhibit 10**);

11. Harlow E, Lane D (1988) Antibodies, A Laboratory Manual. Cold Spring Harbor Laboratory, pages 319 and 322 (**Exhibit 11**);

12. Kennedy MB (1995) Origin of PDZ (DHR, GLGF) domains. Trends Biochem Sci 20: 350 (**Exhibit 12**);

13. Kohler G, Milstein C (1975) Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 256: 495-497 (**Exhibit 13**);

14. Kozbor D, Roder J (1981) Requirements for the establishment of high-titered human monoclonal antibodies against tetanus toxoid using the Epstein-Barr virus technique. J Immunol 127: 1275-1280 (**Exhibit 14**);

15. Kozbor D, Tripputi P, Roder JC, Croce CM (1984) A human hybrid myeloma for production of human monoclonal antibodies. J. Immunol 133: 3001-3005 (**Exhibit 15**);

16. Kiyono T, Hiraiwa A, Fujita M, Hayashi Y, Akiyama T, Ishibasahi M (1997) Binding of high risk papillomavirus E6

oncoproteins to the human homologue of the Drosophila discs large tumor suppressor protein. Proc Natl Acad Sci (USA) 94: 11612-11616 (**Exhibit 16**);

17. Lee SS, Weiss RS, Javier RT (1997) Binding of human virus oncoproteins to hDlg/SAP97, a mammalian homologue of the Drosophila discs large tumor suppressor protein. Proc Natl Acad Sci (USA) 94: 6670-6675 (**Exhibit 17**);

18. Levy R, Miller RA (1983) Tumor therapy with monoclonal antibodies. Fed Proc 42: 2650-2656 (**Exhibit 18**);

19. Nilsson K, Ponten J (1975) Classification and biological nature of established human hematopoietic cell lines. Int J Cancer 15: 321-341 (**Exhibit 19**);

20. Olsson L, Kronstrom H, Cambon-De Mouzon A, Honsik C, Brodin T, Jakobsen B (1983) Antibody producing human-human hybridomas. I. Technical aspects. J Immunol Methods 61: 17-32 (**Exhibit 20**);

21. Östberg L, Pursch E (1983) Human X (mouse X human) hybridomas stably producing human antibodies. Hybridoma 2:361-367 (**Exhibit 21**);

22. Posner MR, Schlossman SF, Lazarus H (1983) Novel approach to construction of human "myeloma analogues" for production of human monoclonal antibodies. Hybridoma 2:369-381 (**Exhibit 22**);

23. Raison RL, Walker KZ, Halnan CR, Briscoe D, Basten A. (1982) Loss of secretion in mouse-human hybrids need not be due to the loss of a structural gene. J Exp Med 156:1380-1389 (**Exhibit 23**);

24. Reading CL (1982) Theory and methods for immunization in culture and monoclonal antibody production. J Immunol Methods 53: 261-291 (**Exhibit 24**);

25. Sahin U, Tureci O, Schmitt H, Cochlovius B, Johannes T, Schmits R, Stenner F, Luo G, Schobert I, Pfreundschuh M (1995) Human neoplasms elicit multiple specific immune responses in the autologous host. Proc Natl Acad Sci (USA) 92: 11810-11813 (**Exhibit 25**);

26. Saras J, Heldin CH (1996) PDZ domains bind carboxy-terminal sequences of target proteins. Trends Biochem Sci 21: 455-458 (**Exhibit 26**);

27. Scanlan MJ, Chen Y-T, Williamson B, Gure AO, Stockert, JD, Gordan O, Tureci O, Sahin U, Pfreundschuh M, Old LJ (1998) Characterization of human colon cancer antigens recognized by autologous antibodies. Int J Cancer 76: 652-658 (**Exhibit 27**);

28. Scanlan MJ, Williamson B, Jungbluth A, Stockert E, Arden KC, Viars CS, Gure AO, Gordan JD, Chen Y-T, Old LJ (1999) Isoforms of the human PDZ-73 protein exhibit differential tissue expression. Biochim Biophys Acta 1445: 39-52 (**Exhibit 28**);

29. Seabright S (1971) Lancet 2: 971-972 (**Exhibit 29**);

30. Shenk T (1996) In: Fields Virology, (editors) Fields BN, Knipe DM, Howley PM (Lippinscott, Philadelphia), Vol 2, pp 2111-2148 (**Exhibit 30**);

31. Shnyra AA et al. (1990) In: Friedman H, Klein TW, Nakano M, Nowotny A, and Eds. Advances in Exp. Medicine & Biology Endotoxin New York: Plenum, 256: 681 (**Exhibit 31**);

32. Teng NN, Lam KS, Calvo Riera F, Kaplan HS (1983) Construction and testing of mouse--human heteromyelomas for human monoclonal antibody production. Proc Natl Acad Sci. (USA) 80: 7308-7312 (**Exhibit 32**);

33. Weiss MC, Green H (1967) Human-mouse hybrid cell lines containing partial complements of human chromosomes and functioning human genes. Proc Natl Acad Sci (USA) 58: 1104-1111 (**Exhibit 33**); and

34. Yunis JJ (1980) Cancer Genetics and Cytogenetics 2: 221-229 (**Exhibit 34**).

Reference 11 listed above was cited in an International Search Report issued February 7, 2003 in connection with International Patent Application No. PCT/US01/29242, a foreign counterpart of the subject application. A copy of this Search Report is attached hereto as **Exhibit D**. The remaining references cited in the Search Report were previously made of record in the subject application, having been cited by the U.S. Patent and Trademark Office in an Office Action dated September 26, 2002.

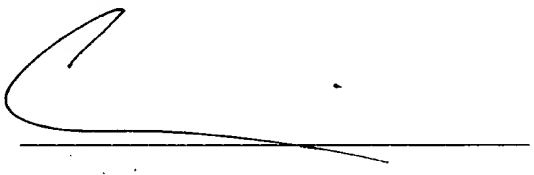
Conclusion

In view of the remarks made herein, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection set forth in the April 30, 2003 Final Office Action and earnestly solicit allowance of all claims pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $543.00 RCE filing fee, is deemed necessary in connection with the filing of this RCE. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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